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Original Research Article

Severity of thrombocytopenia and its outcome in preterm and term neonates admitted in neonatal intensive care unit in a rural tertiary care hospital

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ABSTRACT

Background: Detection of thrombocytopenia is a useful initial assessment for sick neonates, and it is considered as one of the complications of the disease process.
Methods: The present study was a prospective hospital based observational study done in 60 neonates in the department of Paediatrics, KIMS, Narketpally during the period of October 2016 to September 2018.
Results: The proportion of babies with thrombocytopenia admitted to the NICU was 10.9%. out of the sixty newborns with thrombocytopenia, 31(51.7%) were term babies and 29(48.3%) babies were preterm. Out of 29 preterm babies 3 (5%) were extremely preterm, 5 (8.3%) were very preterm and 21(35%) babies were moderate to late preterm. 32 babies (53.3%) had mild thrombocytopenia, 14 babies (23.3%) babies had moderate thrombo cytopenia and 14 babies (23.3%) had severe thrombocytopenia. The most common etiologic association with thrombocytopenia was septicemia (60%) followed by birth asphyxia (23.3%), maternal Pregnancy induced Hypertension (18.3%), both Disseminated intravascular coagulation and Meconium aspiration syndrome were 6.6% and Necrotizing enterocolitis was 3%. Among the 60 babies admitted with thrombocytopenia, the most frequently seen symptom was not feeding well (35%) and lethargy (33.3%) in all three groups that is babies with mild, moderate, and severe thrombocytopenia. Mortality rate among severely thrombocytopenic neonates was significantly higher (57.14%).
Conclusions: Low platelet count was an independent risk factor for poor outcome in our study. Hence it could be used as a prognostic indicator in thrombo- cytopenic neonates.

Keywords: Bleeding, Platelets, Septicemia, Thrombocytopenia

INTRODUCTION

In the newborn low platelet count is a common finding in both preterm and term newborn. 0.7-4% of all neonates have thrombocytopenia. It has been estimated that as many as 22% of all newborns admitted to Neonatal intensive care unit develop low platelet counts. A platelet count of less than 150,000/mm3 is defined as thrombocytopenia irrespective of the age of the individual.[1]

Detection of thrombocytopenia is a useful initial assessment for sick neonates, and it is considered as one of the complications of the disease process, but in some

cases, thrombocytopenia is detected accidentally. Though thrombocytopenia is so prevalent it is often ignored in the assumption that it will resolve spontaneously. However, if it is not detected and managed properly can result in devastating complications.[2]

Coagulation abnormalities and low platelet are common in sepsis, but multiple disease processes can cause thrombocytopenia in neonates and these can be classified as early onset (≤72 hours) and late onset (>72 hours) neonatal thrombocytopenia.[3]

This study was undertaken to analyse the implications of severity of thrombocytopenia and its impact on the outcome in neonates admitted to Kamineni Institute of Medical Sciences, Narketpally, which is a tertiary care hospital in a rural area.

Aim and objectives of this study was as follows,

- to study the severity of thrombocytopenia and its outcome in preterm and term neonates admitted in Neonatal Intensive Care Unit.
- to determine the severity of thrombocytopenia in both preterm and term neonates with thrombocytopenia.
- To evaluate the conditions associated with thrombocytopenia.
- To determine the clinical findings associated with thrombocytopenia in preterm & term neonates in relation to the severity of thrombocytopenia.
- To analyze the outcome of neonates with thrombocytopenia.

METHODS

The present study was a prospective hospital based observational study done in the Neonatal Intensive care unit (NICU), Department of Pediatrics, Kamineni institute of Medical Sciences, Narketpally, Nalgonda Dt. Telangana State.

Duration of study was from October 2016 to September 2018. Study sample was taken from the babies admitted to the Neonatal Intensive Care Unit having a platelet count of< 150000/mm^3. Sample size was of 60 neonates with thrombocytopenia.

Inclusion criteria

- All the neonates admitted in neonatal intensive care unit with a platelet count of <150000 cells/mm^3.

Exclusion criteria

- Neonates with congenital malformations.
- Idiopathic Thrombocytopenic Purpura in mother.

Prior to the start of study, approval of Institutional Ethics Committee of Kamineni Institute of Medical Sciences, Narketpally was taken. A written informed Consent was taken from either of the child ‘s parents/ guardian before enrolling the child for the study.

Statistical analysis

All relevant details related to the cases were entered into the Microsoft Excel. Statistical analysis was performed by using SSPS version 19, p value below 0.05 was taken to be statistically significant.

RESULTS

Total No. of neonates admitted in the Neonatal Intensive Care Unit during the period of October 2016 to September 2018 = 638. No. of neonates with thrombocytopenia (Platelet count< 1,50,000/mm^3) are 70 i.e.10.9% of the babies admitted to NICU had thrombocytopenia. No. of neonates with thrombocytopenia included in the present study after exclusion = 60. No. of preterm babies are 29 and term babies are 31.

In the present study, out of the sixty newborns with thrombocytopenia, 31(51.7%) were term babies (>37 wks of gestation) and 29(48.3%) babies were preterm. Out of 29 preterm babies 3 (5%) were extremely preterm (< 28wks), 5 (8.3%) were very preterm (28-32wks), and 21(35%) babies were moderate to late preterm (32-36 wks 6 days).

In the present study, 32 babies (53.3%) had sever thrombocytopenia, out of which 11(18.3%) were preterm and 21(35%) were term babies and, 14babies (23.3%) had moderate thrombocytopenia, out of which 8(13.3%) were preterm and 6(10%) were term babies and 14babies (23.3%) had mild thrombocytopenia, out of which10 (16.6%) were preterm and 4(6.7%) were term babies.

In the present study out of the 14(23.3%) babies with mild thrombocytopenia, 11(18.3%) babies were male and 3(5%) were female babies. Out of the 14(23.3%) babies with moderate thrombocytopenia, 8(13.3%) were male babies and 6(10%) were female babies. Out of 32(53.4%) babies were severe thrombocytopenia, 17(28.4%) were male babies and 15(25%) were female babies. The differences were not significantly different (Table 1).

In the present study, among the 31 term babies, in the category where 19(61.2%) babies had early onset thrombocytopenia i.e. <72 hours, 16(84.2%) babies had mild thrombocytopenia, and 2(10.5%) babies had moderate and 1(5.2%) baby had severe. Among the term babies with late onset thrombocytopenia (N=12) (38.7%), 5 (41.6%) babies had mild, 4(33.3%) babies had moderate, and 3(25%) babies had severe thrombocytopenia. Among the 29 preterm babies with early onset thrombocytopenia (N=17) (58.6%), 9 (52.9%) babies had mild, 5(26.3%) babies had moderate and 3 (15.7%) babies had severe thrombocytopenia. In the

preterm neonates with late onset thrombocytopenia (N=12), 2(16.6%) babies had mild thrombocytopenia, 3(25%) babies had moderate and 7 (58.3%) had severe thrombocytopenia (Table 2).

Table 1: Distribution of cases based on the severity of thrombocytopenia and sex of child (n=60).

Gender	Mild thrombocytopenia	Moderate thrombocytopenia	Severe thrombocytopenia
Male	11(18.3%)	08(13.3%)	17(28.4%)
Female	3(5%)	6(10%)	15(25%)
	14(23.3%)	14(23.3%)	32(53.4%)

$\chi^2 = 2.69$, p =0.231. (not significant at p <0.05)

Table 2: Distribution of cases based on age of onset in correlation to gestational age n=60.

Gestational age	Onset	Thrombocytopenia			χ^2 p value
		Mild N=32	Moderate N=14	Severe N=14	
Term	Early	16 (84.2%)	2 (10.5%)	1 (5.2%)	
N=31	N=19				*χ^2= 6.11 p=0.047. (significant at p <0.05)
	(61.2%)				
	Late	5 (41.6%)	4 (33.3%)	3 (25%)	
	N=12				
	(38.7%)				
Preterm	Early	9 (52.9%)	5 (26.3%)	3 (15.7%)	
N=29	N=17				*χ^2= 5.87 P=0.053. (not significant at p <0.05)
	(58.6%)				
	Late				
	N=12	2 (16.6%)	3 (25%)	7 (58.3%)	
	(41.3%)				

In the present study, out of the 60 babies with thrombocytopenia, 29 babies were preterm and 31 were term babies. The majority of babies in the study i.e. 36 babies (60%) had septicemia as a cause for thrombocytopenia. Fourteen (23.3%) babies in the study had birth asphyxia, 4(6.6%) babies had disseminated intravascular coagulation, 4(6.6%) babies had meconium aspiration syndrome, 3(5%) babies had necrotizing enterocolitis. Eleven (18.3%) babies having thrombocytopenia, had h/o Maternal PIH. Some babies in the study had multiple causes. The difference in the etiology for thrombocytopenia in preterm and term babies was not significant.

Among 60 babies with thrombocytopenia, 11 babies (18.3%) had a history of PIH in the mother. Among the 11 babies, 5(8.3%) babies had mild thrombocytopenia, 3(5%) babies had moderate thrombocytopenia and 3(5%) babies had severe thrombocytopenia. Out 0f 11 babies born to mothers with PIH, 7(11.6%) are preterm and 4(6.66%) are term babies with thrombocytopenia.

In the present study, among the 60 babies with thrombocytopenia, 12 babies had Bleeding manifestations (20%). Among these, 9(15%) babies were preterm neonates and 3 (5%) were term neonates with bleeding manifestations indicating that babies with thrombocytopenia, are more likely to present with bleeding manifestations, if they are preterm and Lesser is the chance, if baby is term and this difference between the two groups is significant(p value <0.05).

Twelve out of 60 babies (20%) had developed bleeding manifestations at multiple sites including petechiae/ Purpura in 9 preterm babies, and 3 term babies, Gastrointestinal bleed in 7 preterm babies and 2 term babies, and pulmonary bleed in 8 preterm babies and 1 term baby. There were 6 preterm babies with intra cranial bleed, 1 term baby had evidence of intra cranial bleed. Some babies had developed bleeding at multiple sites.

In the present study, out of the 60 babies with thrombocytopenia, in babies with severe thrombocytopenia 10 babies (71.4%) had bleeding manifestation, and in babies with moderate thrombocytopenia 2 babies (14.2%) had bleeding manifestations and majority of babies with moderate thrombocytopenia had no bleeding manifestations.

In babies with mild thrombocytopenia there was no baby with bleeding manifestation, indicating that the severity of thrombocytopenia increased the tendency to bleed.

The outcome of neonates based on the severity of thrombocytopenia was assessed in terms of duration of hospital stay (Table 3).

Table 3: Neonatal outcome-based severity of thrombocytopenia and duration of hospital stay.

Severity of thrombocytopenia	Duration of hospital stay (mean no. of days)
Mild thrombocytopenia N=32	7 days
Moderate thrombocytopenia N=14	9.5 days
Severe thrombocytopenia N=14	16 days
ANOVA test	F Statistics= 9.403, p= 0.0002, significant at p=<0.05)

The outcome in 60 babies admitted with thrombocytopenia was assessed by the mortality. Out of the 60 babies 10 babies (16.6%) died. Among the 10 babies who died, 2(20%) had moderate thrombocytopenia and 8(80%) babies had severe thrombocytopenia. The cause of death in these babies was due to multiple reasons such as Septicaemia, Disseminated intravascular coagulation, Birth asphyxia, Meconium aspiration syndrome, Necrotising enterocolitis, shock. Many of the babies had multiple causes.

The outcome in babies with thrombocytopenia was assessed by the need for platelet transfusion for babies with thrombocytopenia, 12 babies (20%) out of the 60 babies required platelet transfusion. In the babies with severe thrombocytopenia 10 out of the 14 babies (71.4%) required transfusion, whereas in the babies with moderate thrombocytopenia, 2 out of 14(14.2%) babies required platelet transfusion. In the babies with mild thrombocytopenia, no baby needed a transfusion.

Out of the 12 babies requiring platelet transfusion, six babies required more than one unit of platelet transfusion (Table 4).

Table 4: Neonatal outcome based on need for transfusion and severity of thrombocytopenia.

Severity of thrombocytopenia	No. of babies requiring platelet transfusions
Mild thrombocytopenia N=32	None
Moderate thrombocytopenia N=14	2
Severe thrombocytopenia N=14	10
ANOVA test	F Statistics=44.0343, p<0.0001, Significant at p=<0.05)

DISCUSSION

The present study was done in 60 neonates in the department of Paediatrics, KIMS, Narketpally during the period of October 2016 to September 2018. This study was done with the objective of evaluating the severity of thrombocytopenia, its causes, various clinical presentations and outcome in neonates with thrombocytopenia.

Similar studies done on 168 neonates by Bhagawan S. Natani in 2015, at Jaipur on Clinical Outcome of Neonates with Thrombocytopenia.[4] Sharangouda Patil et al, did a study in 2014 in 140 babies at Gulbarga.[5] Beiner ME et al conducted a study on risk factors for neonatal thrombocytopenia in 305 preterm infants in 2003 at Tel-Aviv University, Israel.[6] M.Sandeep et al, (N=60) did a study on Platelet Indices in 60 Neonates in 2015 at Karnataka.[7] Anubha sharma et al, (N=100) did a prospective study on thrombocytopenia In high risk neonates in 2013 at Amritsar.[8] Keerthi tirupathi et al, (N=200) studied about the risk factors of neonatal thrombocytopenia in 2016 at Maharashtra.[9] Ramesh babu et al, (N=100) conducted a study on the clinical profile of neonates with thrombocytopenia in 2014 at Dharmapuri.[10] Lea bonifacio et al, studied thrombocytopenia related outcome in 94 neonates in 2006 at New Jersey.[11] Basil M. Hanoudi et al, studied about the risk factors for neonatal thrombocytopenia in 728 preterm infants in 2015 at Baghdad.[12]

The proportion of babies in the present study was not comparable with the other studies, where a higher proportion of babies were having thrombocytopenia which could be attributed to larger sample size and higher number of preterm's in their study.

The mean gestational age in term group was 38 weeks which was comparable with M. Sandeep et al, study.[7] Mean gestational age in preterm group was 33 weeks compared to 31 weeks in M Sandeep et al study and 34 weeks in Bhagawan et al.[7,4] In the study by Lea Bonafacio et al, the mean GA was 27 weeks this is because the study included only preterm infants of <32wks.

The prevalence of moderate and severe thrombocytopenia in present study was comparable with the study done by S. Patil et al, and Rameshbabu et al.[5,10] In a study done by Anubha Sharma et al, and Keerthi Tirupathi et al, study and Lea bonifacio et al, study there was more number of babies with thrombocytopenia in moderate and severe group.[8,9,11] The higher prevalence of severe thrombocytopenia is probably due to higher proportion of septicemic neonates in NICU admissions.

Male to female ratio in present study was 1.5. The preponderance of male babies in the studies were comparable to studies done by Ramesh Babu et al, Basil Hanoudi where the M:F ratio was 1.17:1, and 1.38:1

respectively and not comparable to the study done by Anubha Sharma where the M:F ratio was 5.21:1.10,12,8 This higher incidence of male children is probably due to the fact that the factors regulating the synthesis of gamma globulin are situated on the X- chromosome and male has only one X-chromosome.

Data wise 60% of the neonates in the present study were diagnosed with thrombocytopenia before 72 hrs of birth and 40% presented after 72hrs age. This is comparable with Patil et al, study (63.5% and 36.5% respectively) and Natani BS et al, study (62.5% and 37.5% respectively).[5]

In the present study, Septicemia was seen in 58.3% cases. Septicemia was strongly associated with thrombocytopenia, especially the severe variety (p=0.008). This finding is in agreement with other studies where septicemia has been recognized to be one of the risk factors for thrombocytopenia in neonates admitted to NICU.[5,11,12] The higher incidence of septicemia in the study done by Lea Bonifaccio and Basil M Haoudi may be due to the fact that they have conducted the studies in preterm babies, who are more susceptible to infection because of their poor immune status compared to the term babies.[11,12]

In the present study 23.3% of babies with thrombocytopenia had a history of birth asphyxia. This finding was comparable with the studies of Ramesh Babu (25%), Keerthi Tirupathi (20%), Basil M Haoudi (28.4%).[10,9,12] Perinatal asphyxia is reported, widely, to be associated with neonatal thrombocytopenia. Perinatal asphyxia was diagnosed based on the following conditions in present study; an arterial pH of 7.34, neonatal neurological manifestation suggestive of HIE, evidence of multiorgan dysfunction. Since we were unable to do cord blood pH the immediate arterial pH (i.e. within 6 hours of birth) was used to diagnose perinatal asphyxia. It has been shown that though postnatally the arterial pH increases the differences between asphyxiated and the non-asphyxiated infants remain significant.

In the present study, DIC was present in 6.67% cases, and this was comparable with study done by Natani BS et al, (5.35%).[4] DIC is known to be initiated by bacterial toxins, such as exotoxins and lipopolysacchride, producing endothelial dysfunction. Quantitative and qualitative differences exist between the toxins secreted by various bacteria. The spectrum of organisms causing neonatal sepsis in this community is different from that in western countries. Hence the type of toxins secreted by the organisms and the frequency of DIC, acquired by virtue of these toxins, might also differ from our community.

In the present study, in the babies admitted with thrombocytopenia, Meconium aspiration syndrome was associated in 6.67% babies. This finding was comparable with the study done by Keerthi Tirupathi who found that 5% of the babies were associated with Meconium aspiration syndrome.[9]

In the present study, out of 60 babies admitted with thrombocytopenia, Necrotising enterocolitis was seen in 5% cases. This finding was comparable with the studies done by Ramesh Babu, Lea Bonifacio, and Basil M Hanoudi, who found NEC in 4%,7%, and 4.21% respectively.[10-12] NEC, as diagnosed by Bell's criteria, was significantly associated with thrombocytopenia in our study($p<0.001$). All the neonates in present study with radiological evidence of NEC had neonatal thrombocytopenia. This finding is in agreement with the well-known fact that thrombocytopenia is one of the major lab markers of NEC.

Maternal PIH was significantly associated with neonatal thrombocytopenia ($P<0.001$). But maternal PIH is associated with mild to moderate thrombocytopenia rather than severe thrombocytopenia in other studies while in present study it was associated with severe thrombocytopenia. This could once again be explained by the frequent exposure of these neonates to infection, due to the relatively high prevalence of septicemia in present study that leads to a precipitous fall in platelet count.

Presence of mucosal bleeding in the present study was 83.33%, and the studies done by Mehta et al, showed 68.23%, Beiner et al, 82.33%, and S Patil 64.70%.[13,6,5] Mucosal bleeding was significantly associated with severity thrombocytopenia The types of bleeding included G.I bleed, bleed from the E.T. tube (pulmonary hemorrhage) and bleeding from the oral cavity. This association reiterates the widely held belief that severely thrombocytopenia neonates are more prone to bleed. The incidence of petechiae and purpura was significantly associated with severe thrombocytopenia ($p<0.001$) with 72% of these neonates having them. This association has been well reported and documented in the past.[11] The most common symptom other than bleeding was "not feeding well". But this symptom is a nonspecific one that can be associated with any sick neonate. Hence, this finding is of not much clinical significance. The most common sign other than bleeding in the severely thrombocytopenic group was delayed capillary refill (>3 sec.). This association might either be due to shock in sick, especially septicemic neonates, who are known to have severe thrombocytopenia or might be due to excessive blood loss. But we couldn't document hypotension due to the unavailability of continuous intra-arterial or oscillometric BP monitoring.

Evidence of intracranial haemorrhage was seen in 7 (11.6%) cases in the present study, which was comparable to study done by Anubha sharma who showed 9.1% of the cases with thrombocytopenia had Intracranial bleeding and in the study done by Jeanette, 12% of the babies with thrombocytopenia had intracranial bleed.[8,14]

The mean duration of hospital stay in babies with mild thrombocytopenia was 7 days. In moderate thrombocytopenia the mean duration was 9.5 days and in severe thrombocytopenia the babies had stayed in the hospital for a period of 16 days. While 87.5% of the severely thrombocytopenic neonates had to stay longer than a week, they also spent more time on IV fluids and supplemental oxygen. This might be related to the severity of the underlying sickness in these neonates and / or due to the increased incidence of complications during their stay. There are no studies comparable with this outcome measure.

The outcome in babies with thrombocytopenia was assessed by the need for platelet transfusion for babies with thrombocytopenia. Twelve (20%) out of the 60 babies required platelet transfusion. In the babies with severe thrombocytopenia 10 out of the 14 babies (71.4%) required transfusion, whereas in the babies with moderate thrombocytopenia, 2 out of 14(14.2%) babies required platelet transfusion. In the babies with mild thrombocytopenia, no baby needed a transfusion. Out of the 12 babies requiring platelet transfusion, six babies required more than one unit of platelet transfusion.

Anubha Sharma in their study demonstrated that 38% of the newborns with thrombocytopenia required platelet transfusions.[8] In the study done by Lea bonifacio et al, seventy three percent of the neonates required platelet transfusion.[11] The higher proportion of platelet transfusion in the study could be attributed to the study being done in neonate of <32 weeks.

In present study out of 60 babies, 10 babies (16.6%) died. Among the 10 babies who died, 2 babies (20%) had moderate thrombocytopenia and 8 babies (80%) babies had severe thrombocytopenia. Mortality was high among the severely thrombocytopenic Neonates. The proportion of a "Non-satisfactory" outcome was more in the mild to moderate thrombocytopenia group. This association might be due to the higher degree of severity of the underlying illness or due to an increased susceptibility of the neonates to complications, in the severely thrombocytopenic group.

In the present study, the proportion of neonates with thrombocytopenia who died was 16.6% and in the study done by Natani BS et al, the mortality was 25%.[4] Ramesh Babu et al, reported only 5% mortality in their cases.[10] This could be due to less number of cases in severe thrombocytopenia group (N=29) in comparison to mild and moderate severity (N=71)

CONCLUSION

The proportion of babies with thrombocytopenia admitted to the Neonatal intensive care unit was 10.9%. Among 60 babies in the study, 32 babies (53.3%) had mild thrombocytopenia, 14 babies (23.3%) babies had moderate thrombocytopenia and 14 babies (23.3%) had severe thrombocytopenia. The most common etiologic association with thrombocytopenia was septicemia (60%), followed by birth asphyxia (23.3%), maternal Pregnancy induced Hypertension (18.3%), Disseminated intravascular coagulation (6.6%) and Meconium aspiration syndrome (6.6%) and Necrotizing enterocolitis was 3%. Twenty percent of the cases developed bleeding manifestations at various sites including skin, GI tract, pulmonary system and intracranial bleed. The most frequently seen symptom was not feeding well (35%) and lethargy (33.3%) which was seen in all three groups, that is babies with mild, moderate, and severe thrombocytopenia.

The mean duration of hospital stay in babies with mild thrombocytopenia was 7 days, in moderate thrombocytopenia was 9.5 days, and in severe thrombocytopenia the mean duration of hospital stay was 16 days, 20% of the 60 babies in the study required platelet transfusions, 10 babies out of 14 (71.4%) required transfusions, the babies with moderate thrombocytopenia, 2 out of 14 (14.2%) babies required platelet transfusions. Ten babies with thrombocytopenia (16.6%) died and 50 were discharged.

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